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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/518,523

Filing Date: August 17, 2005

Appellant(s): HAYNES ET AL.

Mary J. Wilson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 22 December 2009 appealing from the Office action mailed 19 February 2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Ross *et al.* Enhanced Avidity Maturation of Antibody to Human Immunodeficiency Virus Envelope: DNA Vaccination with gp120-C3d fusion proteins. *AIDS Res Hum Retroviruses*. 2001 June 10; Vol. 17(9), p. 829-835.

Shearer *et al.* "Transport of Recombinant Human CD4-1immunoglobulin G across the Human Placenta." *CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY*, Vol. 2, No. 3 (May 1995), pp. 281-285.

Wyatt *et al.* "Involvement of the VI/V2 Variable Loop Structure in the Exposure of Human Immunodeficiency Virus Type 1 gp120 Epitopes Induced by Receptor Binding." *JOURNAL OF VIROLOGY*, Vol. 69, No. 9 (September 1995), pp. 5723-5733.

5518723 DeVico 5-1996

Rizzuto *et al.* "A Conserved HIV gp120 Glycoprotein Structure Involved in Chemokine Receptor Binding." *Science* , Vol. 280 (19 June 1998), pp. 1949-1953.

(9) Grounds of Rejection

The following three grounds of rejection are applicable to the appealed claims:

- I. The rejection of claims 1-12 under 35 U.S.C. §103(a) as being obvious over Ross *et al.* (2001, hereinafter "Ross") in view of Shearer *et al.* (1995, hereinafter "Shearer"), as evidenced by Rizzuto *et al.* (1998), is maintained.

The instant claims are directed to a fusion protein comprising: (i) an IgG Fc component, (ii) an HIV envelope (Env) component, and (iii) a C3d component; and a composition comprising the fusion protein. Claim 2 further limits IgG Fc in the

orientation N-terminal to the HIV Env. Claim 3 further limits HIV Env in the orientation N-terminal to the C3d. Claim 3 further limits the fusion protein to IgG Fc-HIV Env-C3d orientation. Claim 4 further limits the fusion to comprise at least one intervening sequence between at least 2 of said components. Claim 6 further limits IgG Fc to human IgG Fc. Claim 7 further limits C3d to human C3d. Claim 8 recites the property that said C3d component targets said fusion protein to antigen presenting cells that express CD21 and thereby promotes antigen presentation. Claim 9 further limits HIV Env to gp120, gp41, gp160. Claim 10 recites the property that HIV Env comprises residues of the V3 domain of gp120 and includes a B cell neutralizing antibody epitope. Claims 11 and 12 are directed to a composition comprising the fusion protein.

Ross discloses a fusion protein comprising the (ii) component and the (iii) component – a DNA vaccine expressing a fusion protein of murine C3d fused to the C-terminus of HIV Env gp120 (recited in claim 9) that is administered into mice with gold beads as a carrier (recited in claims 11 and 12). See pages 2-3. Ross further discloses that one consequence of complement activation is the covalent attachment of the C3d to antigen. C3d in turn binds to CD21 on B lymphocytes (recited in claim 8) which ultimately amplifies B cell activation and antibody production. See page 2, middle full paragraph.

Ross does not specifically describe a human C3d in the fusion protein of HIV Env gp120 and C3d. However, Ross discloses that in the human immune system, C3d is one of the final degradation products of the third complement protein, C3. See page 2, middle full paragraph. Thus, Ross provides the motivation to make a fusion protein of

HIV Env gp120 and human C3d (recited in claim 7) when the host to be administered the immunogen is changed from mice to human. Since the HIV gp120 is specifically disclosed by Ross, the property that the gp120 protein comprises the V3 domain towards its C-terminus and includes a B cell neutralizing antibody epitope (recited in claim 10) is inherently disclosed, as evidenced by Rizzuto *et al.* (1998).

Ross does not disclose the IgG Fc component of the claimed fusion protein. Shearer discloses a fusion protein by fusing the gp120 binding domain of CD4 to the Fc portion of the human IgG1 (recited in claim 6) heavy chain. See Abstract and page 281. This chimeric protein retains certain properties of human IgG, including a prolonged half-life in serum and Fc receptor binding. See page 281, the sentence connecting the left and right column. Furthermore, Shearer discloses linkers composed of two repeats of four glycines and a serine were fused at the junctions of Env and C3d (recited in claim 5). See page 3, lines 7-8.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Shearer's human IgG Fc component to either the N-terminus (recited in claims 1-4) or the C-terminus of Ross' fusion protein of gp120-C3d for the purpose of increasing the serum half-life of gp120-C3d. One of ordinary skill in the art would have a reasonable expectation of success because Shearer suggests that human IgG Fc prolongs the serum half-life of the fusion partner. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

II. The rejection of claims 13, 14, 16 and 17 under 35 U.S.C. §103(a) as being obvious over *Ross et al.* (2001, hereinafter "Ross") in view of *Shearer et al.* (1995, hereinafter "Shearer") and *DeVico et al.* (US 5,518,723, hereinafter "DeVico"), as evidenced by *Rizzuto et al.* (1998), is maintained.

The instant claims are directed to a complex comprising a fusion protein comprising: (i) an IgG Fc component, (ii) an activated ligand-bound HIV envelope (Env) component, and (iii) a C3d component.

The disclosure of Ross and Shearer is set forth above. Neither reference discloses a ligand-bound HIV Env.

DeVico teaches an immunogen, called gp120-CD4 complex, which is the recombinant HIV envelope protein gp120 chemically crosslinked to a soluble CD4 ligand (column 1, lines 7-12). DeVico further teaches that the gp120-CD4 immunogen exposes cryptic epitopes on gp120 that induces neutralizing antibodies to gp120 (column 7, lines 37-47). Still further, DeVico teaches that the CD4-complexed gp120 appears to undergo a conformational change that present an array of epitopes (recited in claim 13) that were hidden on the uncomplexed glycoprotein. Covalently bonded CD4-gp120 complexes are useful for raising neutralizing antibodies against various isolates of HIV-1 and against HIV-2 (column 1, lines 57-67; column 2, lines 1-2). As evidenced by Rizzuto et al., CD4 binding to HIV gp120 can induce (up-regulate) the CCR5 binding site on gp120, facilitating HIV fusion to a host cell via CCR5 co-receptor (whole document, particularly Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Shearer's human IgG Fc component to either the N-terminus (recited in claims 1-4) or the C-terminus of Ross' fusion protein of gp120- C3d for the purpose of increasing the serum half-life of gp120-C3d, and to further modify the fusion protein by crosslinking a CD4 molecule to the middle component, HIV Env gp120, so as to raise neutralizing antibodies. The skilled artisan would have a reasonable expectation of success because Shearer suggests that human IgG Fc prolongs the serum half-life of the protein that the IgG Fc is fused to and because DeVico teaches that CD4-complexed gp120 raises non-strain-specific neutralizing antibodies against both HIV-1 and HIV-2. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

III. The rejection of claims 13-15 under 35 U.S.C. §103(a) as being unpatentable over Ross *et al.* (2001, hereinafter "Ross") in view of Shearer *et al.* (1995, hereinafter "Shearer") and Wyatt (1995, hereinafter "Wyatt"), as evidenced by Rizzuto *et al.* (1998), is maintained.

The instant claims are directed to a complex comprising a fusion protein comprising: (i) an IgG Fc component, (ii) an HIV envelope (Env) component bound to an antibody, and (iii) a C3d component.

The disclosure of Ross and Shearer is set forth above. Neither reference discloses a ligand-bound HIV Env.

Wyatt discloses a complex comprising HIV gp120 bound to a monoclonal antibody (recited in claim 15), which is shown as the wild-type gp120-17b and wild-type gp120-48d control in precipitation in Figure 2A and B (see also page 5726, right column, last paragraph) and as the wild-type gp120-A32 control in Figure 4 and Figure 5 (see also page 5728, right column). Upon the binding of soluble CD4, HIV gp120 experiences conformational changes and up-regulates (exposes) the conserved, discontinuous epitope on the HIV gp120. The binding of the A32 antibody to the wild type envelope glycoprotein gp120 activates the gp120 so that mAbs 17b and 48d recognize and bind to the exposed conformational epitopes and form the gp120/mAb A32/17b or gp120/mAb A32/48d complex. See page 5728, right column and Figure 5.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Shearer's human IgG Fc component to either the N-terminus (recited in claims 1-4) or the C-terminus of Ross' fusion protein of gp120- C3d for the purpose of increasing the serum half-life of gp120-C3d, and to further modify the fusion protein by binding an antibody to the middle component, HIV Env gp120, so as to raise more neutralizing antibodies, per the suggestion of Wyatt. The skilled artisan would have a reasonable expectation of success because Shearer suggests that human IgG Fc prolongs the serum half-life of the protein that the IgG Fc is fused to and because Wyatt teaches that mAb-complexed gp120 exposes more epitopes for other neutralizing antibodies. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

(10) Response to Argument

Appellant has presented the following arguments: (1) nothing in Ross and/or Shearer would have suggested a fusion protein comprising IgG Fc, gp120 and C3d, nor would the references have provided any factual basis for a reasonable expectation of generating a successful product. (2) Examiner's rationale for combining Ross and Shearer do not constitute the type of reasoning required to support the contention that the combination of references would have led an artisan to the claimed invention. (3) Examiner's conclusion of obviousness is based upon improper hindsight reasoning. (4) Nothing in De Vico *et al.* would have motivated an artisan to combine the teachings thereof with those of Ross *et al.* (relating to DNA vaccination) and Shearer *et al.* (relating to a vertical transmission blocking agent). (5) Nothing in Wyatt *et al* would have motivated an artisan to combine the teachings thereof with those of Ross *et al.* (relating to DNA vaccination) and Shearer *et al.* (relating to a vertical transmission blocking agent).

Appellant's arguments are found unpersuasive. Appellants' arguments have already been addressed in the Final Action mailed on 19 February 2009, which are being reiterated for clarification.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levingood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

Applicant seemed to continuously disregard the cited portions from the Ross and Shearer references and cling to the irrelevant facts, the DNA vaccination in the Ross reference and the vertical HIV transmission in the Shearer reference, of the cited prior art to assert the lack of basis for the combination to arrive at the claimed invention. It is respectfully clarified that Ross discloses and provides the motivation to make a fusion protein of HIV Env gp120 and human C3d (recited in claim 7) because Ross discloses that fusing three copies of murine C3d to the carboxyl terminus of the HIV Env gp120

subunit induces higher antibody responses to Env and a faster onset of avidity maturation than does the wild type gp120 (page 2, third paragraph). In the human immune system, C3d is one of the final degradation products of the third complement protein, C3. One consequence of complement activation is the covalent attachment of the C3d to antigen. C3d in turn binds to CD21 on B lymphocytes, a molecule with B cell stimulatory functions that amplify B lymphocyte activation. Thus, it would be obvious to one skilled in the art to replace the murine C3d with human C3d to induce higher antibody responses to HIV Env gp120 in a human body.

While it is already acknowledged that the cited Ross reference does not teach the exact fusion protein comprising IgG Fc as claimed, Appellant's assertion that Examiner's rationales do not constitute the type of reasoning required to support the combination of references lacks evidentiary basis and reasoning. Furthermore, it is respectfully submitted that Shearer provides the motivation to fuse one more protein component, IgG Fc, to Ross's fusion protein of gp120-C3d because Shearer discloses that fusing IgG Fc to an antigen, gp120-binding domain of the CD4 protein, prolongs the fusion protein's half-life in serum and Fc receptor binding (page 281, see the sentence bridging the two columns). Longer serum half-life means that the antigenic protein remains in the human body longer and induces more antibody responses. Examiner appreciates Applicant's summary of Shearer's study of mother-infant HIV vertical transmission. However, this extraneous fact is not relevant or relied upon for achieving the claimed invention and thus not germane to the rejection at issue. On the other hand, Applicant does not present any showing or scientific reasoning to support her

contention that Examiner's rationale pertaining to the longer serum life and Fc receptor binding does not provide any factual basis for a reasonable expectation of success. Applicant has not explained why these rationales pertaining to extended serum half-life and Fc receptor binding, which in turn leads to higher antibody response, do not constitute the type of reasoning required to support the combination of references leading to the claimed invention. In other words, Applicant has not presented any evidence proving otherwise than the expected advantage and the predictable result of higher antibody response.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicant's argument that nothing in DeVico would have motivated an artisan to combine the teachings thereof with those of Ross and Shearer. It is respectfully reiterated, as set forth in all previous Office Actions, that DeVico provides the motivation to covalently bind CD4 to the gp120 in the fusion protein complex of IgGFc-gp120-C3d as suggested by Ross and Shearer because DeVico discloses that the covalently bonded CD4-gp120 complexes are useful for raising neutralizing

antibodies against various isolates of HIV-1 and against HIV-2. Each modification to Ross' fusion protein of gp120-C3d is for the purpose of raising higher titers of antibody response, as expressly taught by Shearer and DeVico. Therefore, the combination of references in the instant case is properly motivated. Applicant's assertion of no expectation of success in the combination lacks reasoning and/or evidentiary basis. Applicant has not provided any showing to support the contention that nothing in the combination provided basis for expecting success. Applicant has never submitted the scientific reasoning for inoperability of the product according to the way the Examiner combines the prior art teachings. Applicant has never shown why one skilled in the art would not raise higher antibody response if Ross's gp120-C3d fusion protein was modified to the IgG Fc-gp120-C3d fusion, as motivated by Shearer, to achieve a longer serum half-life and better Fc receptor binding (which means longer stimulation of the immune response), and if the fusion protein was further modified to the IgG Fc-gp120=CD4-C3d fusion protein, as motivated by DeVico, to increase the spectrum of immune responses by raising neutralizing antibodies against various isolates of HIV-1 and against HIV-2.

In response to Applicant's argument that nothing in Wyatt would have motivated an artisan to combine the teachings thereof with those of Ross and Shearer. However, as set forth in the previous Office Action, Wyatt provides the motivation to bind monoclonal antibody (mAb) to the gp120 in the fusion protein complex of IgG Fc-gp120-C3d as suggested by Ross and Shearer because Wyatt discloses that mAb-complexed gp120 exposes more epitopes for other neutralizing antibodies. Each modification to

Ross' fusion protein of gp120-C3d is for the purpose of raising higher titers of antibody response, as expressly taught by Shearer and Wyatt.

Applicant repeatedly dismissed Examiner's rationales for the combination of cited prior art as "comments only on the combination of Shearer and Ross and, separately, the combination of Ross and Wyatt, [or] the combination of Ross and DeVico." The expectation of the advantage of raising higher titers of antibody response has been presented as the rationale for combining the cited references. However, Applicant does not support her contention of no expectation of success with any scientific reasoning or evidence such as an immunogenic result that is different from the expected advantage of higher antibody response. If a *prima facie* case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case. See, e.g., *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Rebuttal evidence and arguments can be presented in the specification, *In re Soni* 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), by counsel, *In re Chu*, 66 F.3d 292, 299, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995), or by way of an affidavit or declaration under 37 CFR 1.132, e.g., *Soni* 54 F.3d at 750, 34 USPQ2d at 1687; *In re Piasecki* 745 F.2d 1468, 1474, 223 USPQ 785, 789-90 (Fed. Cir. 1984). However, arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

Therefore, the combination of references in the instant case properly establishes a *prima facie* case of obviousness. Therefore, the rejections of record are considered to be proper.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/L. H./

Examiner, Art Unit 1648

Conferees: (SPE Mondesi and Nickol)

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646

/Robert B Mondesi/

Supervisory Patent Examiner, Art Unit 1645